

**Remarks/Arguments**

Claims 1-15 and 17 are pending in the application. Claims 1-9 and 15 have been withdrawn from consideration pursuant to a lack of unity objection. Claims 10-14 and 17 are therefore under consideration. Reconsideration is requested in view of the above changes and the following remarks.

Claim 10 has been amended to point out that the composition comprises complexes that are extracted from pathogenic bacteria. Support for the amendment is found in the specification at page 9, line 29.

**Response to Rejection Under 35 U.S.C. § 101**

Claims 10-13 and 17 have been rejected under Section 101 as being allegedly drawn to a product of nature. The Examiner alleges that the claims read on heat shock protein complexes in the form in which they may occur in nature. The Examiner alleges that bacterial membranes are known adjuvants and that the cytoplasm of bacteria is a naturally occurring aqueous carrier of the endogenous complex. From these remarks, applicants understand Examiner to assert that the claims read on intact bacteria.

Claim 10 has been amended to more particularly point out and define the invention as a composition that contains heat shock protein/antigenic peptide fragment complexes that are *extracted* from bacteria. Manifestly, if the composition comprises complexes that are extracted from bacteria, the composition can not itself be a bacterium. Thus, claim 10 does not recite a product of nature.

Claim 11 is directed to a composition prepared according to a two step process. In a first step, pathogenic bacteria are manipulated to induce the formation of heat shock protein/antigenic peptide fragment complexes. In a second step, the complexes are extracted from the bacteria to form the claimed composition. Since the composition of claim 11 comprises complexes extracted from a bacteria, the composition is not itself a bacterium. Thus, neither claim 11, nor its dependent claims 12, 13 and 17, recite a product of nature.

Response to Rejections Under 35 U.S.C. § 102

Srivastava (US Patent No 5,961,979) - Rejection Under 35 U.S.C. § 102(e)

The Examiner has maintained the rejection of claims 10-14 and 17 as allegedly anticipated by Srivastava (US Patent No 5,961,979). Applicant respectfully submits that the claims are not anticipated by Srivastava for the following reasons.

The examiner states: "It is the position of the examiner that Srivastava discloses compositions that comprise Bacteria/*E.coli* heat shock protein-peptide complexes from bacteria through disruption of the bacterial pathogen and then naturally purified and include peptides that originate from the pathogen itself" (see col. 6, lines 12-13; col.6, lines 65-68 and col. 7, line 7)." Applicant has difficulty understanding the meaning of this sentence, and the point that Examiner is attempting to make through the sentence. It is respectfully submitted that the point has not been conveyed in a clear and concise manner. Applicant will thus respond based on what applicant considers the apparent meaning of the sentence.

Srivastava does not disclose the claim element "one or more endogenous complexes ... between an induced heat shock protein which is derived from the pathogenic bacteria and an antigenic peptide fragment which is also derived from the pathogenic bacteria". Although Srivastava teaches stress protein/peptide complexes, the stress protein component of the complex is not derived from a pathogenic bacteria. Rather, the stress protein component of the complex is derived from a eukaryotic cell. Srivastava at no time teaches or suggests that the stress protein component can be derived from a pathogenic bacteria.

Examiner notes that Srivastava teaches at column 5, line 56 and column 11, lines 43 to 46, that the stress proteins DnaK and Hsp70 are derived from *E. coli*. However, mention of these stress proteins is for the purpose of exemplifying how widely the function of stress proteins is conserved across species barriers, rather than suggesting that such stress proteins could be used in the formation of complexes, as in the present invention.

The referenced portion of Srivastava beginning at column 5, line 57 relates to a mere diatribe on stress proteins. The stress proteins mentioned in the discussion are disclosed to make the point that stress proteins are found in all prokaryotes and eukaryotes. The purpose

of that Srivastava disclosure is not to list what stress proteins are provided in complexes, and certainly not the complexes of the invention. Examiner has incorrectly selecting portions of the Srivastava description which are not inter-related and conjoined them to provide an argument and come to a conclusion that both the stress protein and the peptide component of a complex can be derived from a pathogenic bacteria. The conclusion is not justified from the totality of the reference's teaching, which must be considered. *See, W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303, 311 (Fed.Cir.1983), *cert. denied*, 469 US 851 (1984).

This fact (i.e. that at no point does Srivastava consider that the stress protein complex can be formed using a stress protein other than one derived from a eukaryotic cell, and most definitely not from a prokaryotic cell) is also seen throughout the description of Srivastava. For example, column 6, lines 22 to 25 reads "In a preferred aspect of the invention a stress protein belonging to the Hsp90 family, namely gp96 can be used to generate an effective vaccine containing a gp96-peptide complex". The gp96 stress protein is a mammalian stress protein.

Further, Srivastava column 8 states that "In one approach, the stress protein-peptide complex may be harvested from any sample of tissue, isolated cell or immortalized cell line infected with the preselected intracellular pathogen...". As such, there is again (i) no consideration that the stress protein-peptide complex can be derived from a bacterial pathogen, and (ii) no consideration or acknowledgement that a stress-protein peptide complex which is derived solely from a bacterial pathogen would have utility in the invention of Srivastava.

Furthermore, column 8, lines 18 to 53 discuss the production of synthetically prepared stress-protein peptide complexes. It is specifically taught that "the antigenic peptide may be eluted from either a purified stress-protein complex...". It is then stated that "Stress proteins may be purified directly from cells naturally expressing the stress proteins". This is followed by "The two purified components may then be combined in vitro to generate a synthetic and completely defined stress-protein complex". If Srivastava had known or appreciated that a stress-protein peptide complex derived from a pathogenic bacteria could itself be used in a vaccine composition to induce an immune response against the pathogen from which the

complex was derived, then there would have been absolutely no requirement to generate the antigenic peptide component and the stress-protein of the component of the complex individually and conjoin them together. Hence, the stated step of purifying stress proteins would not have been necessary. Rather it would only have been necessary to purify stress-protein peptide complexes.

These differences further reinforce how different the presently claimed invention is to the teachings of Srivastava, and how the present invention does not fall within the teaching of Srivastava. Why would Srivastava go to the bother of obtaining a peptide fragment and a stress protein independently and then combine them together to form a complex if it were known to him that all that was required was to obtain a stress-protein peptide complex from a pathogen?

Examples indicating Srivastava at no point considered that the stress protein component of the complex could be derived from a pathogenic bacteria cell, or that both the stress-protein and the peptide component of the complex could be both derived from the same cell, are found elsewhere in Srivastava.

Column 9, lines 24-27 teaches that "The invention is based on the discovery that a stress protein-peptide complex isolated from a *eukaryotic* cell infected with a preselected intracellular pathogen when administered to a mammal can stimulate a cytotoxic T cell response" (emphasis added). This again shows that there was no consideration by Srivastava that a pathogenic bacteria would have been suitable for the production of the stress-protein, for inclusion in the complexes of the present invention.

Column 10, lines 20-30 states: "The peptide may be any amino acid sequence that is present in a *eukaryotic* cell infected with an intracellular pathogen but not present when the cell is not infected with the same pathogen" and further that "The immunogenic complexes may be purified from any *eukaryotic* cells, including: whole tissues, isolated cells; and immortalized eukaryotic cell lines transfected with the intracellular pathogen" (emphasis added). Once again, there is no teaching or suggestion that a pathogenic bacteria can be the source of the stress-protein which form the immunogenic complexes of Srivastava.

Column 12, lines 14-20 states: "It has been discovered that the stress protein-peptide complexes of the invention can be prepared from cells infected with intracellular pathogens as well as cells that have been transformed by an intracellular pathogen. For example, immunogenic stress protein peptide-complexes may be isolated from *eukaryotic* cells transformed with a transforming virus such as SV40..." (emphasis added). Again, the use of pathogenic bacteria is not considered. Furthermore, pathogenic bacteria would not be suitable for being infected with an intracellular pathogen or being transformed. \*

Column 12, line 53 onwards teaches the propagation of infected eukaryotic cells. There is no equivalent example relating to prokaryotic cells. The example mentions the propagation of HIV-I virus in human CD4+ T cells, the propagation of influenza virus in human fibroblast cells and MDCK cells, and the culturing of mycobacteria in Schwaan cells. The use of a eukaryotic cell component within which an intracellular pathogen can grow is clearly essential. Srivastava gives no consideration or example relating to a cell where the eukaryotic host cell is not present. The host cell is always considered essential to allow the stress protein peptide complexes to be formed.

A case where a pathogenic bacteria, such as mycobacteria, is grown in a host cell is highlighted by the examiner as being a situation where, following lysis of the cell, a complex comprising a stress protein-peptide complex from the bacteria could be provided. However, according to the methods of Srivastava, this would not occur. Specifically, the use of a dounce homogenizer, as taught at column 13, line 63, would not be effective to cause the pathogenic bacteria which were infecting the host cell to be lysed or broken up. As such, the "other cell debris" referred to at column 13, line 65 would contain the pathogenic bacteria and the bacteria stress protein/peptides complexes therein. Hence, these would not be present in the supernatant.

For the foregoing reasons, claims 10-14 and 17 are not anticipated by Srivastava.

Phipps et al. (1991, EMBO J., 10:1711-1722) - Rejection Under 35 U.S.C. § 102(b)

Examiner has maintained the rejection of claims 10-14 and 17 as allegedly anticipated by Phipps *et al.* (“Phipps”) Applicant respectfully submits that the claims are not anticipated by Phipps, for the following reasons.

Applicant submits that the teachings of Phipps are not relevant to the novelty of the claims. The disclosure of Phipps is concerned with ATPase activity, which is assayed by ATP addition. As noted in the present application, ATP disassembles stress protein-peptide complexes, such that the stress protein and the peptide components are no longer associated.

Under point 5 of page 5 of the Detailed Action, Examiner refers to two bands of 57 kDa molecular and 62 kDa molecular weight in the gel of Phipps Figure 10. These bands represent heat shock proteins only. That is, they do not represent heat shock proteins complexed to peptides to form a stress protein-peptide complex.

The stress protein-peptide complex of the presently claimed invention is a two component system. Such a complex is not clearly and unambiguously shown in Phipps. Rather, the examiner is reaching conclusions which cannot be supported by the teachings of Phipps. Having identified sections of the disclosure of Phipps which indicate that the proteins produced in Phipps in response to stress are stress proteins which may fall within the meaning of a stress protein of the instant claims, the examiner has assumed that the stress protein is part of a stress protein-peptide complex. Such a complex is simply not taught by Phipps.

For these reasons, it is respectfully submitted that Phipps does not anticipate claims 10-14 and 17.

Wawrzynow et al. (1991, EMBO J., 9:1867-1877) - Rejection Under 35 U.S.C. § 102(b)

Examiner has maintained the rejection of claims 10 and 11 as allegedly anticipated by Wawrzynow *et al.* (“Wawrzynow”) Applicant respectfully submits that claims 10 and 11 are not anticipated by Wawrzynow, for the following reasons.

Wawrzynow fails to contain any disclosure of the following claim feature: “one or more endogenous complexes ... between an induced heat shock protein which is derived from

the pathogenic bacteria and an antigenic peptide fragment which is also derived from the pathogenic bacteria”.

It appears that in considering the teaching of Wawrzynow, the Examiner has only consider whether something equivalent to a stress protein is produced, and not whether a stress protein peptide complex according to the instantly claimed invention is present.

The fact that Wawrzynow raised antibodies to ClpX only shows that ClpX is present. There is absolutely no evidence or suggestion provided in Wawrzynow that the ClpX is associated with a peptide to form a stress protein/peptide complex. The examiner is therefore, once again, extrapolating information from the reference which is, quite simply, not taught. Furthermore, the  $\lambda$ O protein which the examiner suggests may be complexed to ClpX is derived from a bacteriophage, *i.e.* a virus which infects a bacteria. This is not a peptide derived from a pathogenic bacteria as required by the instant claims. As such, it is respectfully submitted that claims 10 and 11 are not anticipated by Wawrzynow.

#### Response to Obviousness-Type Double Patenting Rejection

Applicant requests that the provisional non-statutory obviousness-type double patenting rejection be held in abeyance until claims have actually issued or are deemed allowable in copending Application No. 10/363,454.

#### Status of Application No. 10/363,454

As Examiner has stated that the application contains subject matter related to Application No. 10/363,454, the status of that application is as follows.

Substantive office actions were mailed on the following dates: May 1, 2006; July 26, 2007; and Aug. 18, 2008. Prior art asserted in the rejections include the following: WO 96/40928; and Narberhaus. *Molecular Microbiology*, 31(1):1-8 (1999).

An information disclosure statement identifying the above references, and the other references of record from Application No. 10/363,454, is submitted herewith.

Conclusion

The claims remaining in the application are believed in condition for allowance. An early action toward that end is earnest solicited.

Respectfully submitted

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